



PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

Andrew P. THOMAS et al.

Application No.: 10/698,388

Filed: November 3, 2003

FOR: QUINAZOLINE DERIVATIVES AND
PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM

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)
) Confirmation No. 2735
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) Examiner: Patel, S.
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Date: December 17, 2004

Sir:

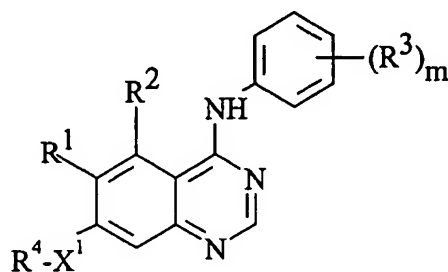
AMENDMENT UNDER 37 C.F.R. § 1.312

This Amendment under 37 C.F.R. § 1.312 is being filed to physically incorporate the structure of formula I and associated definitions from allowed method claim 17 into allowed method claims 18 and 20, in place of the reference to formula I. The amendment is for purposes of clarification, and does not, and is not intended to, change the substance or scope of claims 18 and 20. Entry of this amendment after allowance is therefore believed to be appropriate and entry thereof is respectfully requested.

IN THE CLAIMS:

Claims 1-16 (canceled).

Claim 17 (previously presented): A method for producing an anti-cancer effect in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of formula I:



(I)

wherein:

m is an integer from 1 to 2;

R¹ represents hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylthio, or -NR⁵R⁶ (wherein R⁵ and R⁶, which may be the same or different, each represents hydrogen or C₁₋₃alkyl);

R² represents hydrogen, hydroxy, halogeno, methoxy, amino or nitro;

R³ represents hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino or nitro;

X¹ represents -CH₂-, -S-, -SO-, -SO₂-, -NR⁷CO-, -CONR⁸-, -SO₂NR⁹-, -NR¹⁰SO₂- or -NR¹¹- (wherein R⁷, R⁸, R⁹, R¹⁰ and R¹¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

R⁴ is selected from one of the following twelve groups:

- 1) C₁₋₅alkylR¹² (wherein R¹² is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to C₁₋₅alkyl through a carbon atom and which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl,

C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl,

N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl) or C₁₋₅alkylR¹³

(wherein R¹³ is a group selected from pyrrolidin-1-yl, imidazolidin-1-yl and

thiomorpholino, which group may bear one or two substituents selected from oxo,

hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl,

C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and

C₁₋₄alkoxycarbonyl);

- 2) C₂₋₅alkenylR¹⁴ (wherein R¹⁴ is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 3) C₂₋₅alkynylR¹⁵ (wherein R¹⁵ is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 4) C₁₋₅alkylX²C₁₋₅alkylX³R¹⁶ (wherein X² and X³ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR¹⁷CO-, -CONR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents hydrogen or C₁₋₃alkyl) with the proviso that X¹ cannot be -CH₂- when R⁴ is C₁₋₅alkylX²C₁₋₅alkylX³R¹⁶;
- 5) C₁₋₅alkylX⁴COR²² (wherein X⁴ represents -O- or -NR²³- (wherein R²³ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²² represents -NR²⁴R²⁵ or -OR²⁶ (wherein R²⁴, R²⁵ and R²⁶ which may be the same or different each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 6) C₁₋₅alkylX⁵R²⁷ (wherein X⁵ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR²⁸CO-, -CONR²⁹-, -SO₂NR³⁰-, -NR³¹SO₂- or -NR³²- (wherein R²⁸, R²⁹, R³⁰, R³¹ and R³² each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) or X⁵ is carbonyl, and R²⁷ represents cyclopentyl, cyclohexyl or a 5 or 6 membered saturated

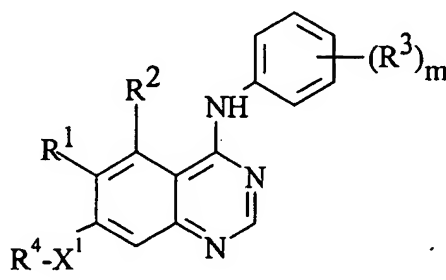
heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which cyclopentyl, cyclohexyl or heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl or R²⁷ is C₁₋₃alkyl with the proviso that when R²⁷ is C₁₋₃alkyl, X⁵ is -S-, -SO-, -SO₂-, -SO₂NR³⁰- or -NR³¹SO₂- and X¹ is not -CH₂-);

- 7) C₁₋₃alkoxyC₂₋₄alkyl provided that X¹ is -S-, -SO- or -SO₂-;
- 8) C₁₋₅alkylX⁶C₁₋₅alkylR³³ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴CO-, -CONR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³³ represents cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which cyclopentyl, cyclohexyl or heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 9) R³⁹ (wherein R³⁹ is a group selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl which group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 10) C₁₋₅alkylR⁴⁰ (wherein R⁴⁰ is piperazin-1-yl which bears at least one substituent selected from C₁₋₄alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₄hydroxyalkyl and -CONR⁴¹R⁴² (wherein R⁴¹ and R⁴² each independently represents hydrogen or C₁₋₄alkyl);
- 11) C₁₋₅alkylR⁴³ (wherein R⁴³ is morpholino which may bear one or two substituents selected from oxo, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl) with the proviso that when R⁴ is C₁₋₅alkylR⁴³, X¹ is -S-, -SO-, -SO₂-, -SO₂NR⁹- or -NR¹⁰SO₂-; and

12) C₁₋₅alkylR⁴⁴ (wherein R⁴⁴ is morpholino which bears at least one and optionally two substituents selected from oxo, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof.

Claim 18 (currently amended): A method for inhibiting the effects of VEGF in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective inhibiting amount of a quinazoline derivative of formula I:



(I)

wherein:

m is an integer from 1 to 2;

R¹ represents hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylthio, or -NR⁵R⁶ (wherein R⁵ and R⁶, which may be the same or different, each represents hydrogen or C₁₋₃alkyl);

R² represents hydrogen, hydroxy, halogeno, methoxy, amino or nitro;

R³ represents hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino or nitro;

X¹ represents -CH₂-, -S-, -SO-, -SO₂-, -NR⁷CO-, -CONR⁸-, -SO₂NR⁹-, -NR¹⁰SO₂- or -NR¹¹- (wherein R⁷, R⁸, R⁹, R¹⁰ and R¹¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

R⁴ is selected from one of the following twelve groups:

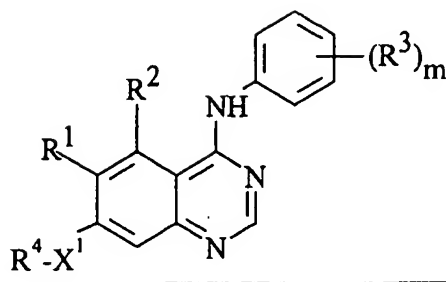
- 1) C₁₋₅alkylR¹² (wherein R¹² is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to C₁₋₅alkyl through a carbon atom and which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl) or C₁₋₅alkylR¹³ (wherein R¹³ is a group selected from pyrrolidin-1-yl, imidazolidin-1-yl and thiomorpholino, which group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 2) C₂₋₅alkenylR¹⁴ (wherein R¹⁴ is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 3) C₂₋₅alkynylR¹⁵ (wherein R¹⁵ is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 4) C₁₋₅alkylX²C₁₋₅alkylX³R¹⁶ (wherein X² and X³ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR¹⁷CO-, -CONR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents hydrogen or C₁₋₃alkyl) with the proviso that X¹ cannot be -CH₂- when R⁴ is C₁₋₅alkylX²C₁₋₅alkylX³R¹⁶;
- 5) C₁₋₅alkylX⁴COR²² (wherein X⁴ represents -O- or -NR²³- (wherein R²³ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²² represents -NR²⁴R²⁵ or -OR²⁶

- (wherein R^{24} , R^{25} and R^{26} which may be the same or different each represents hydrogen, C_{1-4} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 6) C_{1-3} alkyl X^5R^{27} (wherein X^5 represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR²⁸CO-, -CONR²⁹-, -SO₂NR³⁰-, -NR³¹SO₂- or -NR³²- (wherein R^{28} , R^{29} , R^{30} , R^{31} and R^{32} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) or X^5 is carbonyl, and R^{27} represents cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which cyclopentyl, cyclohexyl or heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, carbamoyl, C_{1-4} alkylcarbamoyl, N,N-di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkanoyl and C_{1-4} alkoxycarbonyl or R^{27} is C_{1-3} alkyl with the proviso that when R^{27} is C_{1-3} alkyl, X^5 is -S-, -SO-, -SO₂-, -SO₂NR³⁰- or -NR³¹SO₂- and X^1 is not -CH₂-);
- 7) C_{1-3} alkoxy C_{2-4} alkyl provided that X^1 is -S-, -SO- or -SO₂-;
- 8) C_{1-3} alkyl X^6C_{1-5} alkyl R^{33} (wherein X^6 represents -O-, -S-, -SO-, -SO₂-, -NR³⁴CO-, -CONR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R^{34} , R^{35} , R^{36} , R^{37} and R^{38} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{33} represents cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which cyclopentyl, cyclohexyl or heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, carbamoyl, C_{1-4} alkylcarbamoyl, N,N-di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkanoyl and C_{1-4} alkoxycarbonyl);
- 9) R^{39} (wherein R^{39} is a group selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl which group may bear one or two substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, carbamoyl, C_{1-4} alkylcarbamoyl, N,N-di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkanoyl and C_{1-4} alkoxycarbonyl);

- 10) C₁₋₅alkylR⁴⁰ (wherein R⁴⁰ is piperazin-1-yl which bears at least one substituent selected from C₁₋₄alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₄hydroxyalkyl and -CONR⁴¹R⁴² (wherein R⁴¹ and R⁴² each independently represents hydrogen or C₁₋₄alkyl);
- 11) C₁₋₅alkylR⁴³ (wherein R⁴³ is morpholino which may bear one or two substituents selected from oxo, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl) with the proviso that when R⁴ is C₁₋₅alkylR⁴³, X¹ is -S-, -SO-, -SO₂-, -SO₂NR⁹- or -NR¹⁰SO₂-; and
- 12) C₁₋₅alkylR⁴⁴ (wherein R⁴⁴ is morpholino which bears at least one and optionally two substituents selected from oxo, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- or a pharmaceutically acceptable salt thereof. ~~or a pharmaceutically salt thereof.~~

Claim 19 (previously presented): A method for inhibiting the effects of VEGF and EGF in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective inhibiting amount of a quinazoline derivative of formula I as claimed in claim 18 or a pharmaceutically acceptable salt thereof.

Claim 20 (currently amended): A method for inhibiting the growth of a solid tumour of the colon, breast, prostate, lung or skin in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective inhibiting amount of a quinazoline derivative of formula I:



wherein:

m is an integer from 1 to 2;

R¹ represents hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylthio, or -NR⁵R⁶ (wherein R⁵ and R⁶, which may be the same or different, each represents hydrogen or C₁₋₃alkyl);

R² represents hydrogen, hydroxy, halogeno, methoxy, amino or nitro;

R³ represents hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino or nitro;

X¹ represents -CH₂-, -S-, -SO-, -SO₂-, -NR⁷CO-, -CONR⁸-, -SO₂NR⁹-, -NR¹⁰SO₂- or -NR¹¹- (wherein R⁷, R⁸, R⁹, R¹⁰ and R¹¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

R⁴ is selected from one of the following twelve groups:

- 1) C₁₋₅alkylR¹² (wherein R¹² is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to C₁₋₅alkyl through a carbon atom and which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl) or C₁₋₅alkylR¹³ (wherein R¹³ is a group selected from pyrrolidin-1-yl, imidazolidin-1-yl and thiomorpholino, which group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl,

C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);

- 2) C₂₋₅alkenylR¹⁴ (wherein R¹⁴ is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 3) C₂₋₅alkynylR¹⁵ (wherein R¹⁵ is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);
- 4) C₁₋₅alkylX²C₁₋₅alkylX³R¹⁶ (wherein X² and X³ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR¹⁷CO-, -CONR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents hydrogen or C₁₋₃alkyl) with the proviso that X¹ cannot be -CH₂- when R⁴ is C₁₋₅alkylX²C₁₋₅alkylX³R¹⁶;
- 5) C₁₋₅alkylX⁴COR²² (wherein X⁴ represents -O- or -NR²³- (wherein R²³ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²² represents -NR²⁴R²⁵ or -OR²⁶ (wherein R²⁴, R²⁵ and R²⁶ which may be the same or different each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 6) C₁₋₅alkylX⁵R²⁷ (wherein X⁵ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR²⁸CO-, -CONR²⁹-, -SO₂NR³⁰-, -NR³¹SO₂- or -NR³²- (wherein R²⁸, R²⁹, R³⁰, R³¹ and R³² each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) or X⁵ is carbonyl, and R²⁷ represents cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which cyclopentyl, cyclohexyl or heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl or R²⁷ is C₁₋₃alkyl with the proviso that when

R²⁷ is C₁₋₃alkyl, X⁵ is -S-, -SO-, -SO₂-, -SO₂NR³⁰- or -NR³¹SO₂- and X¹ is not -CH₂-;

7) C₁₋₃alkoxyC₂₋₄alkyl provided that X¹ is -S-, -SO- or -SO₂-;

8) C₁₋₅alkylX⁶C₁₋₅alkylR³³ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴CO-, -CONR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³³ represents cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which cyclopentyl, cyclohexyl or heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);

9) R³⁹ (wherein R³⁹ is a group selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl which group may bear one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);

10) C₁₋₅alkylR⁴⁰ (wherein R⁴⁰ is piperazin-1-yl which bears at least one substituent selected from C₁₋₄alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₄hydroxyalkyl and -CONR⁴¹R⁴² (wherein R⁴¹ and R⁴² each independently represents hydrogen or C₁₋₄alkyl);

11) C₁₋₅alkylR⁴³ (wherein R⁴³ is morpholino which may bear one or two substituents selected from oxo, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl) with the proviso that when R⁴ is C₁₋₅alkylR⁴³, X¹ is -S-, -SO-, -SO₂-, -SO₂NR⁹- or -NR¹⁰SO₂-; and

12) C₁₋₅alkylR⁴⁴ (wherein R⁴⁴ is morpholino which bears at least one and optionally two substituents selected from oxo, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄alkanoyl and C₁₋₄alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof.

Claim 21 (previously presented): The method according to claim 20 wherein the tumour is of the colon.

Claim 22 (previously presented): The method according to claim 20 wherein the tumour is of the lung.

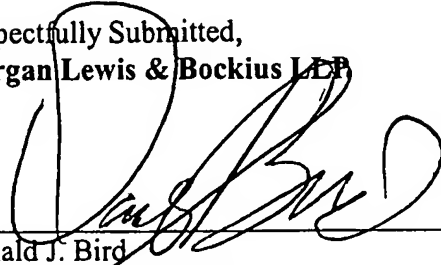
REMARKS

Claims 18 and 20 have been amended by physically inserting therein the structure of formula I and the associated definitions taken from claim 17. On final review of these claims prior to paying the issue fee, it was noted that independent method claims 17, 18 and 20 all referred to "the quinazoline derivative of formula I," but the structure and definitions of formula I were recited only in claim 17. Therefore, for completeness of the claims, the structure of formula I and the associated definitions have been exactly copied from claim 17, and inserted in each of claims 18 and 20.

This amendment does not, and is not intended to, change the scope or substance of claims 18 and 20 in any respect and is being made for purposes of clarification and completeness. It is believed that the review and entry of this amendment does not require any significant effort on the part of the Examiner. Accordingly, it is appropriate to make this amendment after allowance, and entry of the same is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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